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Low solubility drug-coated bead compositions.

Low solubility drug coated bead compositions, capsules filled therewith and method of preparation thereof, especially wherein the low solubility drug is an antiandrogenic steroid and most especially wherein the antiandrogenic steroid is (5α,17α)-1'-(methylsulfonyl)-1'H-pregn-20-yno[3,2-c]pyrazol-17-ol are disclosed.

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The invention relates to low solubility drug-coated bead compositions, capsules filled therewith, and method of preparation thereof, especially wherein the low solubility drug is an antiandrogenic steroid and most especially wherein the antiandrogenic steroid is (5α,17α)-1'-(methylsulfonyl)-1'H-pregn-20-yno[3,2-c]-pyrazol-17-ol.

Harrison et al U.S. Pat. 4,717,569 describes pharmaceutical compositions for oral administration of a polycyclic medicament having a solubility in water and aqueous media at ambient temperatures of less than 1 part of the medicament in from 5,000 to greater than 10,000 parts by weight of the medium which comprises a plurality of beads, each bead comprising particles of finely divided solid medicament bound together by a binder soluble in water and aqueous media at all pH values normally found in the gastrointestinal tract and preferably a pharmacologically acceptable wetting agent, said plurality of beads together constituting a unit dose. In a preferred embodiment, the unit dosage form is enclosed in a gastric juice-soluble material such as gelatin. The beads can be sugar starch beads. The compositions are described as having been prepared by coating the beads with an aqueous suspension of the medicament and binder and optional wetting agent and then encapsulated.

Five examples are described wherein the medicament is 17α-pregna-2,4-diene-20-yno[2,3-d]isoxazol-17-ol (Compound A) and the binder is hydroxypropylmethylcellulose, one in which no wetting agent is included, four in which sodium lauryl sulphate is included as wetting agent, and three in which polyvinylpyrrolidone (PVP) is included as a second binding agent. Improved human bioavailability of the medicament is shown by favorable comparison of several described formulations with corresponding conventional starch-lactose-talc-magnesium stearate dry powder capsule formulations.

Christiansen et al. U.S. Pat. 4,684,636 describes antiandrogenic sulfonylsteroidoxazoles including (5α,17α)-1'-(methylsulfonyl)-1'H-pregn-20-yno[3,2-c]pyrazol-17-ol as the product of Example 1 and pharmaceutical compositions thereof in general including those for oral administration in solid dosage form including capsules and tablets. Conventional pharmaceutically acceptable vehicles and techniques are used in preparing these dosage forms. The patent does not describe any such composition specifically.

According to one aspect of the present invention there are provided sugar or sugar starch beads coated with from about 10% to about 300% by weight of a coating composition consisting essentially of from about 1% to about 80% by weight of a drug having a solubility of less than 1% by weight in water and from about 1% to about 30% by weight each of

(a) a cellulose derivative selected from the group consisting of hydroxypropyl cellulose and hydroxypropyl methylcellulose,

(b) a polyethylene glycol or derivative thereof selected from the group consisting of a polyethylene glycol having a molecular weight from about 1,000 to about 8,000 and d-alpha tocopheryl polyethylene glycol 1000 succinate whose polyethylene glycol part has an average formula weight of about 1,000, and

(c) a waxy solid selected from the group consisting of the polyoxyethylene-polyoxypropylene-polyoxyethylene block copolymer having the structural formula

$$HO(CH_2CH_2O)_a[CH(CH_3)CH_2O]_b(CH_2CH_2O)_aH \qquad \text{Formula I}$$

wherein a has a value of about 79 and b has a value of about 28 and having an average molecular weight from 7680 to 9510, sulfobutanedioic acid 1,4-bis(2-ethylhexyl) ester sodium salt, and sulfuric acid monododecyl ester sodium salt.

In a preferred aspect of the invention the cellulose derivative is hydroxypropyl methylcellulose, the polyethylene glycol or derivative thereof is a polyethylene glycol having a molecular weight from about 1,000 to about 8,000 and the waxy solid is the polyoxyethylene-polyoxypropylene-polyoxyethylene block copolymer of Formula I, wherein a has a value of about 79 and b has a value of about 28 which has an average molecular weight from 7680 to 9510.

In a further aspect the invention relates to a pharmaceutical capsule filled with from about 40 mg to about 700 mg of the above drug-coated bead composition.

Preferably the compositions and capsules of the invention are prepared for oral administration.

According to another aspect of the invention the drug-coated bead composition may be prepared by dissolving the cellulose derivative, the polyethylene glycol or derivative thereof and the waxy solid in water, suspending the drug in the resulting solution with agitation, coating the beads with the resulting suspension and drying the resulting coated beads. Preferably the components are dissolved in from about three to about ten times their combined weight of water, most preferably with warming.

The low solubility drug can be any drug having a solubility of less than 1% by weight in water and is especially a steroid and more particularly an androgenic, antiandrogenic, estrogenic, antiestrogenic, progestational, antiprogestational or cortical steroid including even more particularly a fertility regulant including

contraceptive, metabolism regulant including anabolic, antiinflammatory, antiendometriosis, antiprostatohypertrophia or antiprostatocarcinoma steroid or any steroid having any combination of these properties. The antiandrogenic sulfonylsteroidopyrazoles of above-cited Christiansen et al. U.S. Pat. 4,684,636, including especially (5α,17α)-1'-(methylsulfonyl)-1'H-pregn-20-yno-[3,2-c]pyrazol-17-ol, in particular for treatment of benign prostatic hyperplasia and prostatic carcinoma, are preferred. The preferred amount of drug is from about 40% to about 80% by weight of the coating composition.

The other substances used to prepare the drug-coated bead composition of the invention are known pharmaceutical or food ingredients and, with the exception of d-alpha tocopheryl polyethylene glycol 1000 succinate whose polyethylene glycol part has an average formula weight of about 1,000, those used to prepare the below-described examples are described by The United States Pharmacopeia (USP), Twenty-second Revision and The National Formulary (NF), Seventeenth Edition (a single volume also entitled 1990 USP XXII NF XVII, copyright by United States Pharmacopeial Convention, Inc., 12601 Twinbrook Parkway, Rockville, MD 20852, 1989). The substances used to prepare the drug-coated bead composition of the invention are described under the following names:-Docusate Sodium (USP, p. 471), Hydroxypropyl Methylcellulose (USP, pp. 670-671), Purified Water (USP, p. 1457), Hydroxypropyl Cellulose (NF, p. 1938), Poloxamer (NF, pp. 1960-1961), Polyethylene Glycol (NF, pp. 1961-1963), Sodium lauryl Sulfate (NF, pp. 1980-1981), Sugar Spheres (NF, p. 1989).

Docusate Sodium is described as butanedioic acid, sulfo-, 1,4-bis-(2-ethylhexyl) ester, sodium salt and sodium 1,4-bis(2-ethylhexyl) sulfosuccinate containing not less than 99.0% and not more than 100.5% of $C_{20}H_{37}NaO_7S$, calculated on the anhydrous basis.

Hydroxypropyl Methylcellulose is described as cellulose, 2-hydroxypropyl methyl ether and as a propylene glycol ether of methylcellulose, which when dried at 105 °C for 2 hours contains methoxy (OCH_3) and hydroxypropoxy ($OCH_2CHOHCH_3$) groups conforming to certain limits. Hydroxypropyl Methylcellulose 2910 is the preferred hydroxypropyl methylcellulose of the invention and has a minimum of 28.0% and a maximum of 30.0% of methoxy groups and a minimum of 7.0% and a maximum of 12.0% of hydroxypropoxy groups. Specifications are set forth for three other variants which are designated by the numbers 1828, 2208 and 2906.

Purified Water is described as obtained by distillation, ion-exchange treatment, reverse osmosis or other suitable process and as prepared from water complying with the regulations of the federal Environmental Protection Agency with respect to drinking water and contains no added substance.

Hydroxypropyl Cellulose is described as cellulose, 2-hydroxypropyl ether and as a partially substituted poly(hydroxypropyl) ether of cellulose. It may contain not more than 0.60% silica or other suitable anticaking agents. When dried at 105° for 3 hours, it contains not more than 80.5% hydroxypropoxy groups.

Poloxamer is described as a synthetic block copolymer of ethylene oxide and propylene oxide having the structural formula

$$HO(C_2H_4O)_a(C_3H_6O)_b(C_2H_4O)_aH$$

wherein a and b have the following values for representative variants

Poloxamer	a	b
124	12	20
188	79	28
237	64	37
338	141	44
407	101	56

The average molecular weight is not less than 95.0% and not more than 105.0% of the labeled nominal value if the labeled nominal value is below 1000, it is not less than 90.0% and not more than 110.0% of the labeled nominal value if the labeled nominal value is between 1000 and 7000, it is not less than 87.5% and not more than 112.5% of the labeled nominal value if the labeled nominal value is above 7000.

Polyethylene glycols having nominal average molecular weights in the range from 300 to 8000 are described. Polyethylene Glycol 3350 is the preferred polyethylene glycol of the invention.

Sodium Lauryl Sulfate is also named as sulfuric acid monododecyl ester sodium salt and sodium monododecyl sulfate and is described as a mixture of sodium alkyl sulfates consisting chiefly of sodium lauryl sulfate [$CH_3(CH_2)_{10}CH_2OSO_3Na$]. The combined content of sodium chloride and sodium sulfate is not more than 8.0%.

d-Alpha tocopheryl polyethylene glycol 1000 succinate is described by the manufacturer (Eastman Chemical Products, Inc., a division of Eastman Kodak Company, Kingsport, Tennessee 37662) in a product brochure dated February 4, 1983 as prepared from crystalline d-Alpha Tocopheryl Acid Succinate NF by esterification of the acid group with polyethylene glycol 1000, as also being named Vitamin E TPGS, as being a pale yellow waxy solid having a specific gravity at 45°C of approximately 1.06 and a m.pt. of approximately 40°C and in the opinion of the manufacturer as being recognized as safe ("GRAS") when used as an oral dietary supplement of vitamin E.

The preferred amount of each of the cellulose derivative, polyethylene glycol or derivative thereof and waxy solid in the drug-coated bead composition of the invention is from about 5% to about 30% by weight of the coating composition.

The preferred amount of each of the hydroxypropyl methylcellulose, polyethylene glycol and polyoxyethylene-polyoxypropylene-polyoxyethylene block copolymer in the preferred drug-coated bead composition of the invention is from about 5% to about 15% by weight of the coating composition.

Sugar Spheres are described as containing not less than 62.5% and not more than 91.5% of sucrose ($C_{12}H_{22}O_{11}$) calculated on the dried basis, the remainder consisting chiefly of starch and as consisting of approximately spherical particles of a labeled nominal size range and correspond to the sugar or sugar starch beads of the invention. They can also be or be referred to as granules, particles, pellets or nonpareils and are from about 2 mm or about 10 mesh to about 0.2 mm or about 80 mesh, preferably from about 20 mesh to about 70 mesh, in diameter or longest dimension before coating. After coating the preferred diameter or longest dimension is from about 16 mesh to about 60 mesh.

The capsule shell of the invention which contains the drug-coated bead composition can be any pharmaceutically acceptable capsule shell but is preferably a gelatine capsule shell,which may be soft but is preferably a hard capsule shell, and is of suitable size for containing from about 40 mg to about 700 mg of the drug-coated bead composition of the invention. Conventional machinery and techniques are used in filling the capsule shells.

In the dissolution step of the process of the invention the temperature of warming can be in the range from room temperature to about 100°C, preferably from 50°C to 60°C. About 80% of the total amount of water needed is used for the dissolution and suspension steps and the remainder is used for rinsing the last amounts of solution and suspension from the equipment. Preferably the polyethylene glycol or derivative thereof and the waxy solid are dissolved first and the cellulose derivative is then added and dissolved. The low solubility drug is added to the resulting solution with agitation to form a suspension. The dissolution and suspension steps are carried out with conventional mixing equipment. The suspension is preferably passed through a colloid mill before carrying out the coating step and agitation is maintained during the coating step. The coating and drying steps are preferably carried out in a fluid bed processor with inlet air temperature in the range from 50°C to 70°C with preheating of the sugar or sugar starch beads. After drying the coated beads are sifted to produce coated beads of the desired particle size, preferably 16 to 60 mesh.

The invention will now be more particularly described with relation to the following Examples, which in no way limit the scope of the invention.

Example 1

Ingredient	Amount (kg)
(5α,17α)-1'-(Methylsulfonyl)-1'H-pregn-20-yno[3,2-c]pyrazol-17-ol	0.720
Poloxamer 188, NF	0.090
Polyethylene Glycol 3350, NF	0.144
Hydroxypropyl Methylcellulose 2910, USP	0.100
Sugar Spheres (30-35 mesh), NF	0.450
Purified Water, USP (removed during processing)	(2.460)
Total amount of dry ingredients	~1.500

A portion of this composition sufficient to provide 200 mg of the steroid drug when filled into a hard gelatin capsule has the following composition.

Ingredient	mg/Capsule
(5α,17α)-1'-(Methylsulfonyl)-1'H-pregn-20-yno[3,2-c]pyrazol-17-ol	200.0
Poloxamer 188, NF	25.0
Polyethylene Glycol 3350, NF	40.0
Hydroxypropyl Methylcellulose 2910, USP	27.8
Sugar Spheres (30-35 mesh), NF	125.0
Total Capsule Fill Weight	~418.0

The amount of drug in each capsule can be varied by varying the capsule fill weight, the amount of drug in the coating composition or the amount of coating composition coated onto the sugar or sugar starch beads.

The composition of Example 1 was shown to have improved bioavailability over a conventional tablet composition of the same drug when compared in the dog.

The following conventional tablet composition was prepared using a conventional tablet preparation method.

Comparative Example

Ingredient	mg/Tablet
(5α,17α)-1'-(Methylsulfonyl)-1'H-pregn-20-yno[3,2-c]pyrazol-17-ol	50.0
Microcrystalline Cellulose, NF (Avicel pH 101)	60.0
Poloxamer 188, NF (Pluronic F68)	6.0
Lactose, NF (Spray Dried)	161.5
Croscarmellose Sodium, NF (Ac-Di-Sol)	15.0
Magnesium Stearate, NF	1.5
Povidone, USP (PVP K29-32)	6.0
Total	300.0

Example 2

In separate [illegible] 50 mg [illegible] (5α,17α)-1'-(methylsulfonyl)-1'H-pregn-[illegible]

[illegible]

Composition	Mean C_{max} (µg/ml)(s.d.)	Mean AUC $_{0-\infty}$ (µg-hr/ml)(s.d.)
Comparative Example	0.23 (0.11)	1.70 (1.64)
Example 1	0.40 (0.08)	3.40 (1.3)

Claims

1. Sugar or sugar starch beads coated with from about 10% to about 300% by weight of a coating composition consisting essentially of from about 1% to about 80% by weight of a drug having a solubility of less than 1% by weight in water and from about 1% to about 30% by weight each of
   (a) a cellulose derivative selected from the group consisting of hydroxypropyl cellulose and hydroxypropyl methylcellulose,
   (b) a polyethylene glycol or derivative thereof selected from the group consisting of a polyethylene glycol having a molecular weight from about 1,000 to about 8,000 and d-alpha tocopheryl polyethylene glycol 1000 succinate whose polyethylene glycol part has an average formula weight of about 1,000, and
   (c) a waxy solid selected from the group consisting of the polyoxyethylene-polyoxypropylene-polyoxyethylene block copolymer having the structural formula

   $$HO(CH_2CH_2O)_a[CH(CH_3)CH_2O]_b(CH_2CH_2O)_aH \quad \text{Formula I}$$

   wherein a has a value of about 79 and b has a value of about 28 and having an average molecular weight from 7680 to 9510, sulfobutanedioic acid 1,4-bis(2-ethylhexyl) ester sodium salt, and sulfuric acid monododecyl ester sodium salt.

2. Sugar or sugar starch beads as claimed in claim 1, in which the cellulose derivative is hydroxypropyl methylcellulose, the polyethylene glycol is one having a molecular weight from about 1,000 to about 8,000 and the waxy solid is the polyoxyethylene-polyoxypropylene-polyoxyethylene block copolymer having the structural formula

   $$HO(CH_2CH_2O)_a[CH(CH_3)CH_2O]_b(CH_2CH_2O)_aH \quad \text{Formula I}$$

   wherein a has a value of about 79 and b has a value of about 28, and having an average molecular weight from 7680 to 9510.

3. Coated sugar or sugar starch beads as claimed in claim 2 wherein the hydroxypropyl methylcellulose is designated 2910 and the polyethylene glycol has a molecular weight of about 3350.

4. Coated sugar or sugar starch beads as claimed in any one of the preceding claims wherein the drug is an antiandrogenic steroid.

5. Coated sugar or sugar starch beads as claimed in claim 4, wherein the antiandrogenic steroid is (5α,17β)-1'-methylsulfonyl-1'H-pregn-20-yno [3,2-c]pyrazol-17-ol.

6. Coated sugar or sugar starch beads as claimed in any one of the preceding claims, wherein the amount of drug is from about 40% to about 80% by weight of the coating composition.

7. Coated sugar or sugar starch beads as claimed in any one of the preceding claims, wherein the amount of each of the cellulose derivative, the polyethylene glycol or derivative thereof and the waxy solid is from about 5% to about 30% by weight of the coating composition.

8. Coated sugar or sugar starch beads as claimed in claim 2,wherein the amount of each of the hydroxypropyl methylcellulose, polyethylene glycol and polyoxyethylene-polyoxypropylene-polyoxyethylene block copolymer is from about 5% to about 15% by weight of the coating composition.

9. A pharmaceutical capsule filled with from about 40 mg to about 700 mg of the coated sugar or sugar starch beads as defined in claim 1.

10. A pharmaceutical capsule filled with from about 40 mg to about 700 mg of the coated sugar or sugar starch beads as defined in any one of claims 2 to 9.

11. A process of preparing coated sugar or sugar starch beads as defined in any one of the preceding claims which comprises dissolving the cellulose derivative, the polyethylene glycol or derivative thereof and the waxy solid in water, suspending the drug in the resulting solution with agitation, coating the beads with the resulting suspension and drying the resulting coated beads.

12. A process as claimed in claim 11 wherein the drug is as defined in either of claims 4 and 5.

13. A process of preparing coated sugar or sugar starch beads as defined in any one of claims 2, 3 and 8 which comprises dissolving the hydroxypropyl methylcellulose, the polyethylene glycol and the polyoxyethylene-polyoxypropylene-polyoxyethylene block copolymer in water, suspending the drug in the resulting solution with agitation, coating the beads with the resulting suspension and drying the resulting coated beads.

14. A process of preparing coated sugar or sugar starch beads as defined in any one of claims 11 to 13, in which the cellulose derivative, the polyethylene glycol or derivative thereof and the waxy solid are dissolved in from about three to about ten times their weight in water with warming.

Claims for the following Contracting State : GR

1. A process of preparing sugar or sugar starch beads coated with from about 10% to about 300% by weight of a coating composition consisting essentially of from about 1% to about 80% by weight of a drug having a solubility of less than 1% by weight in water and from about 1% to about 30% by weight each of

(a) a cellulose derivative selected from the group consisting of hydroxypropyl cellulose and hydroxypropyl methylcellulose,

(b) a polyethylene glycol or derivative thereof selected from the group consisting of a polyethylene glycol having a molecular weight from about 1,000 to about 8,000 and d-alpha tocopheryl polyethylene glycol 1000 succinate whose polyethylene glycol part has an average formula weight of about 1,000, and

(c) a waxy solid selected from the group consisting of the polyoxyethylene-polyoxypropylene-polyoxyethylene block copolymer having the structural formula

$$HO(CH_2CH_2O)_a[CH(CH_3)CH_2O]_b(CH_2CH_2O)_aH \quad \text{Formula I}$$

wherein a has a value of about 79 and b has a value of about 28 and having an average molecular weight from about 7680 to 9510, [illegible] butanedioic acid 1,4-bis(2-ethylhexyl) ester sodium salt and sulfuric acid monododecyl ester sodium salt,

which comprises dissolving the cellulose derivative, the polyethylene glycol or derivative thereof and the waxy solid in water, suspending the drug in the resulting solution with agitation, coating the beads with the resulting suspension and drying the resulting coated beads.

2. A process of preparing sugar or sugar starch beads as claimed in claim 1, in which the cellulose derivative is hydroxypropyl methylcellulose, the polyethylene glycol is one having a molecular weight from about 1,000 to about 8,000 and the waxy solid is the polyoxyethylene-polyoxypropylene-polyoxyethylene block copolymer having the structural formula

3. A process of preparing coated sugar or sugar starch beads as claimed in claim 2, wherein the hydroxypropyl methylcellulose is designated 2910 and the polyethylene glycol has a molecular weight of about 3350.

4. A process of preparing coated sugar or sugar starch beads as claimed in any one of the preceding claims, wherein the drug is an antiandrogenic steroid.

5. A process of preparing coated sugar or sugar starch beads as claimed in claim 4, wherein the antiandrogenic steroid is (5α,17α)-1'-(methylsulfonyl)-1'H-pregn-20-yno[3,2-c]pyrazol-17-ol.

6. A process of preparing coated sugar or sugar starch beads as claimed in any one of the preceding claims, wherein the amount of drug is from about 40% to about 80% by weight of the coating composition.

7. A process of preparing coated sugar or sugar starch beads as claimed in any one of the preceding claims, wherein the amount of each of the cellulose derivative, the polyethylene glycol or derivative thereof and the waxy solid is from about 5% to about 30% by weight of the coating composition.

8. A process of preparing coated sugar or sugar starch beads as claimed in claim 2, wherein the amount of each of the hydroxypropyl methylcellulose, polyethylene glycol and polyoxyethylene-polyoxypropylene-polyoxyethylene block copolymer is from about 5% to about 15% by weight of the coating composition.

9. A process of preparing coated sugar or sugar starch beads as claimed in any one of the preceding claims, in which the cellulose derivative, the polyethylene glycol or derivative thereof and the waxy solid are dissolved in from about three to about ten times their weight in water with warming.

Claims for the following Contracting State : ES

1. A process of preparing sugar or sugar starch beads coated with from about 10% to about 300% by weight of a coating composition consisting essentially of from about 1% to about 80% by weight of a drug having a solubility of less than 1% by weight in water and from about 1% to about 30% by weight each of

(a) a cellulose derivative selected from the group consisting of hydroxypropyl cellulose and hydroxypropyl methylcellulose,

(b) a polyethylene glycol or derivative thereof selected from the group consisting of a polyethylene glycol having a molecular weight from about 1,000 to about 8,000 and d-alpha tocopheryl polyethylene glycol 1000 succinate whose polyethylene glycol part has an average formula weight of about 1,000, and

(c) a waxy solid selected from the group consisting of the polyoxyethylene-polyoxypropylene-polyoxyethylene block copolymer having the structural formula

$$HO(CH_2CH_2O)_a[CH(CH_3)CH_2O]_b(CH_2CH_2O)_aH \quad \text{Formula I}$$

wherein a has a value of about 79 and b has a value of about 28 and having an average molecular weight from about 7680 to 9510, sulfobutanedioic acid 1,4-bis(2-ethylhexyl) ester sodium salt, and sulfuric acid monododecyl ester sodium salt

which comprises dissolving the cellulose derivative, the polyethylene glycol or derivative thereof and the waxy solid in water, suspending the drug in the resulting solution with agitation, coating the beads with the resulting suspension and drying the resulting coated beads.

2. A process of preparing sugar or sugar starch beads as claimed in claim 1, in which the cellulose derivative is hydroxypropyl methylcellulose, the polyethylene glycol is one having a molecular weight from about 1,000 to about 8,000 and the waxy solid is the polyoxyethylene-polyoxypropylene-polyoxyethylene block copolymer having the structural formula

$$HO(CH_2CH_2O)_a[CH(CH_3)CH_2O]_b(CH_2CH_2O)_aH \quad \text{Formula I}$$

wherein a has a value of about 79 and b has a value of about 28 and having an average molecular weight from 7680 to 9510

which comprises dissolving the hydroxypropyl methylcellulose, the polyethylene glycol and the polyoxyethylene-polyoxypropylene-polyoxyethylene block copolymer in water, suspending the drug in the resulting solution with agitation, coating the beads with the resulting suspension and drying the resulting coated beads.

3. A process of preparing coated sugar or sugar-starch beads as claimed in claim 2 wherein the hydroxypropyl methylcellulose is designated 2910 and the polyethylene glycol has a molecular weight of about 3350.

4. A process of preparing coated sugar or sugar-starch beads as claimed in any one of the preceding claims wherein the drug is an antiandrogenic steroid.

5. A process of preparing coated sugar or sugar-starch beads as claimed in claim 4, wherein the antiandrogenic steroid is (5α,17α)-1'-(methylsulfonyl)-1'H-pregn-20-yno[3,2-c]pyrazol-17-ol.

6. A process of preparing coated sugar or sugar-starch beads as claimed in any one of the preceding claims wherein the amount of drug is from about 40% to about 80% by weight of the coating composition.

7. A process of preparing coated sugar or sugar-starch beads as claimed in any one of the preceding claims, wherein the amount of each of the cellulose derivative, the polyethylene glycol or derivative thereof and the waxy solid is from about 5% to about 30% by weight of the coating composition.

8. A process of preparing coated sugar or sugar-starch beads as claimed in claim 2, wherein the amount of each of the hydroxypropyl methylcellulose, polyethylene glycol and polyoxyethylene-polyoxypropylene-polyoxyethylene block copolymer is from about 5% to about 15% by weight of the coating composition.

9. A process of preparing coated sugar or sugar-starch beads as claimed in any one of the preceding claims in which the cellulose derivative, the polyethylene glycol or derivative thereof and the waxy solid are dissolved in from about three to about ten times their weight in water with warming.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 92 20 1317

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	EP-A-0 012 523 (AMERICAN HOME PRODUCTS)	1-3, 11-14	A61K9/16 A61K9/50
Y	* claims 1,2,6 * * page 6, line 1 - line 26 * * page 7, line 4 - line 8 * * page 7, line 19 - line 22 * * page 8, line 1 - line 6 * * page 9, line 13 - line 16 * * page 10, line 24 - line 32 *	4-10	
Y	EP-A-0 207 375 (STERLING DRUG INC.) * claims 1,9,10 * * page 37, line 16 - page 38, line 8 *	4-10	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A61K

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	17 JULY 1992	VENTURA AMAT A.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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